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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,957	HERWEIJER ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 2 July 2004 in response to the Non-Final Office Action mailed 8 April 2004. Claims 13-24 and 28-33 were withdrawn from consideration and claims 1-12 and 25-27 were considered in the 8 April Office Action. Claims 13-24 and 28-33 were canceled and claims 1-6, 9, 12 and 25-27 were amended in the 2 July Paper. Claims 1-12 and 25-27 are presently pending and under consideration.

Response to Amendment

Specification

The amendments to the specification filed with the 2 July Paper have not been entered because the instructions for amending the specification are not consistent with its present status. Applicant instructs that "60/xxx,xxx" on page one of the specification be replaced with "60/248,275, filed on November 14, 2000". However, the first line of the specification as originally filed already contains the phrase "60/248,275, filed on November 14, 2000".

The amendment also instructs that the brief description of Figures 3 and 4 be inserted "On page 22, following:--(intravascular delivery of plasmid DNA). -- on line 2". However, line 2 on page 22 does not contain the phrase "(intravascular delivery of plasmid DNA)"

In view of the non-entry of the amendment to the specification, the disclosure stands objected to for the reasons of record. Resubmission of the amendment with proper instructions would overcome this objection.

Appropriate correction is required.

Claim Objections

Objection to claims 25 and 26 as containing informalities is withdrawn in view of the claim amendments.

Claim Rejections - 35 USC § 112

Rejection of claims 1-12, 25 and 26 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the claim amendments.

Double Patenting

Provisional rejection of claims 1, 10, 12 and 26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 66 of copending Application No. 10/202,858 is withdrawn in view of the claim amendments.

Claim Rejections - 35 USC § 102

Rejection of claims 1-3, 6-12 and 25-27 as being anticipated by Jones *et al.*; claims 1-3, 6-12, 25 and 27 as being anticipated by Chen *et al.*; claims 1, 2, 4, 10-12 and 26 as being anticipated by Fu *et al.*; claims 1, 2, 7, 10-12 and 25 as being anticipated by Gregoriadis *et al.*; claims 1, 2, 4, 7, 10-12, 25 and 26 as being anticipated by Ishii *et al.*; claims 1-3, 6-12, 25 and 27 as being anticipated by Roy *et al.*; claims 1-12, 25 and 27 as being anticipated by Guy *et al.*; claims 1-4, 6-12, 25 and 27 as being anticipated by Compans; claims 1-3, 5, 7, 10-12, 25 and 26 as being anticipated by Content *et al.*; and claims 1-3, 5, 7, 10-12 and 25 as being anticipated by Donnelly *et al.* is withdrawn in view of the amendments to the claims.

New Grounds Necessitated by Amendment

Claim Objections

Claims 1 and 25 are objected to because of the following informalities: The claims contain typographical errors. Specifically, in claim 1, part (d), the phrase, "thereby delivering said nucleic acid sequence is to an extravascular cell in said tissue" should be, "thereby delivering said nucleic acid sequence to an extravascular cell in said tissue". In claim 25, the sentence ends with a semicolon instead of a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*,

650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed…If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

The instant claim 1, which previously recited, "[providing] a nucleic acid sequence encoding a peptide containing at least one *antigenic determinant*" (emphasis added) has been amended to read, "providing a nucleic acid sequence encoding a peptide containing a *determinant of said antigen*" (emphasis added). An "antigenic determinant" is a term of art, which is understood to mean an immunogenic portion of a protein or other molecule. In contrast, it would seem that a determinant of an antigen could be anything that determines some unspecified property of the antigen. The originally filed disclosure contains no reference to "a determinant of an antigen" and no teaching that would imply a contemplated "determinant of an antigen". Therefore the limitation constitutes new matter. Claims 2-12 are rejected insofar as they depend from claim 1.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claim is directed to a method of vaccination comprising intravascular delivery of an enteric coated nucleic acid.

State of the prior art and level of predictability in the art: The art contains no teachings specifically directed to intravascular delivery of enteric coated molecules. However, Clymer *et al.* US Patent No. 2,540,979 teaches that enteric coatings are specially designed to protect an orally ingested medicament against release in the stomach and provide selective release in the alkaline environment of the small intestine (see especially column 1). Given that enteric coatings are designed to be insoluble at neutral pH and tend to provide large aggregates, the skilled artisan would not expect to be able to successfully practice the claimed invention with an enteric coated nucleic acid.

Amount of direction provided by the inventor and existence of working examples: The specification provides no working example or instruction with regard to intravenous delivery of an enteric coated nucleic acid.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not expect to be able to practice the claimed invention with an enteric coated nucleic acid without having to engage in undue experimentation to develop an enteric coating suitable for intravenous delivery. Therefore, claim 8 fails to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 9-12, 25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Liu *et al.* (1999) *Gene Ther.* 6:1258-1266 or Zhang *et al.* (1999) *Hum. Gene Ther.* 10:1935-1737, both of which were published July 1999.

Liu *et al.* teaches a method comprising providing a plasmid DNA encoding an antigenic peptide (*i.e.*, luciferase; demonstrated in Example 5, page 41-42, of the instant application to be antigenic), injecting the nucleic acid into a vessel connected to a tissue of a mammal (*i.e.*, a mouse tail vein), elevating intravascular pressure and increasing permeability, thereby delivering

said nucleic acid sequence to an extravascular cell in said tissue (see especially the paragraph bridging the left and right columns on page 1265, and Figures 1-4 and 6-8). Although Liu *et al.* does not explicitly teach inducing an immune response, Liu *et al.* teaches expression of luciferase in various organs and tissues of mice, which is demonstrated in Example 5 of the instant application to elicit an antibody immune response. The specification teaches that the antibody response obtained by the method, "is not surprising given the large amount of antigen that is produced" (page 41, line 20-21). Thus, absent evidence to the contrary, the skilled artisan would expect inducing an immune response to be inherent to the method of Liu *et al.* Therefore, the method of Liu *et al.* meets all of the limitations of independent claims 1 and 25, and dependent claims 9-12 and 27. Furthermore, Liu *et al.* teaches that expression of the luciferase transgene was present in all organs tested, including a liver cell according to claim 5 (see especially Figure 6 and the caption thereto). Given this wide distribution and absent evidence to the contrary, the skilled artisan would expect that the plasmid is delivered to a lymphoid cell, according to claim 2, to a gut or nasal associated lymphoid cell, according to claims 3 and 4, and to a muscle cell according to claim 6.

The method of genetic immunization taught by Liu *et al.* comprises all of the elements of the method of the instant claims; therefore, the limitations of the claims are met by Liu *et al.*

Zhang *et al.* teaches a method comprising providing a plasmid DNA encoding an antigenic peptide (*i.e.*, luciferase; demonstrated in Example 5, page 41-42, of the instant application to be antigenic), injecting the nucleic acid into a vessel connected to a tissue of a mammal (*i.e.*, a mouse tail vein), elevating intravascular pressure and increasing permeability,

thereby delivering said nucleic acid sequence to an extravascular cell in said tissue (see especially the final paragraph on page 1735 through the first paragraph on page 1736 and Figures 1 and 2). Although Zhang *et al.* does not explicitly teach inducing an immune response, Zhang *et al.* teaches expression of luciferase in mice, which is demonstrated in Example 5 of the instant application to elicit an antibody immune response. Thus, absent evidence to the contrary, the skilled artisan would expect inducing an immune response to be inherent to the method of Zhang *et al.* Therefore, the method of Zhang *et al.* meets all of the limitations of independent claims 1 and 25, and dependent claims 9-12 and 27. Furthermore, Zhang *et al.* demonstrates delivery of the plasmid to a liver cell according to claim 5, and the teachings of Liu *et al.* evidence that the method of Zhang *et al.* would provide delivery of the nucleic acid throughout the body (*Id*). Given this wide distribution and absent evidence to the contrary, the skilled artisan would expect that the plasmid is delivered to a lymphoid cell, according to claim 2, to a gut or nasal associated lymphoid cell, according to claims 3 and 4, and to a muscle cell according to claim 6.

Thus, the method of genetic immunization taught by Zhang *et al.* comprises all of the elements of the method of the instant claims; therefore, the limitations of the claims are met by Zhang *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu *et al.* or Zhang *et al.* as applied to claims 1 and 25 above, respectively, and further in view of Smyth-Templeton *et al.* (1998) WO 98/07408.

The claims are directed to the method of genetic immunization described above, wherein the nucleic acid delivered is protected by a coating (claim 7) or is complexed with a polymer. Liu *et al.* and Zhang *et al.* teach a method comprising all of the limitations of the claims (*Id.*) except that Liu *et al.* and Zhang *et al.* teach the method using naked DNA.

Smyth-Templeton *et al.* teaches a polymeric lipid composition specially designed to improve delivery of intravenously administered nucleic acids to cells in animals (see especially

the abstract and the paragraph bridging pages 3-4). Smyth-Templeton *et al.* teaches that lipidic particles increase the efficiency of DNA delivery into cells (see especially the paragraph bridging 1-2) and that the lipid formulations disclosed therein provide particularly efficient delivery of DNA administered intravenously (see especially the paragraph bridging pages 3-4 and Figures 1 and 2 and the captions thereto).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Liu *et al.* or Zhang *et al.* to include complexing the administered plasmid with the protective polymeric coating of Smyth-Templeton *et al.* As described above, Smyth-Templeton *et al.* teaches that lipid complexes generally provide improved delivery of nucleic acids into cells, and that the formulations disclosed therein are particularly well suited for delivery of nucleic acids by intravenous administration. Given these teachings and the general desirability of obtain the most efficient delivery of DNA possible implied throughout each of the Liu *et al.*, Zhang *et al.* and Smyth-Templeton *et al.* publications, the skilled artisan would be motivated to combine the teachings to provide improved efficiency of DNA delivery *in vivo*.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because Smyth-Templeton *et al.* demonstrates the effectiveness of nucleic acid delivery using the complexes by tail vein injection in mice (see especially Example 4) and there is no reason to expect that the elevated pressure used in the methods of Liu *et al.* and Zhang *et al.* would in any way affect the complexes of Smyth-Templeton *et al.*

In view of these considerations, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time of filing based on the teachings of Liu *et al.* or Zhang *et al.* in view of Smyth-Templeton *et al.*

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER